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**Structure of the GAF Domain, a Ubiquitous Signaling Motif and a New Class of Cyclic GMP Receptor**

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**ABSTRACT:** GAF domains are ubiquitous motifs present in cyclic GMP (cGMP)-regulated cyclic nucleotide phosphodiesterases, certain adenylyl cyclases, the bacterial transcription factor FhlA, and hundreds of other signaling and sensory proteins from all three kingdoms of life. The crystal structure of the *Saccharomyces cerevisiae* YKG9 protein was determined at 1.9 Å resolution. The structure revealed a fold that resembles the PAS domain, another ubiquitous signaling and sensory transducer. YKG9 does not bind cGMP, but the isolated first GAF domain of phosphodiesterase 5 binds with  $K_d = 650$  nM. The cGMP binding site of the phosphodiesterase GAF domain was identified by homology modeling and site-directed mutagenesis, and consists of conserved Arg, Asn, Lys and Asp residues. The structural and binding studies taken together show that the cGMP binding GAF domains form a new class of cyclic nucleotide receptors distinct from the regulatory domains of cyclic nucleotide-regulated protein kinases and ion channels.